

Formation of stoichiometric and non-stoichiometric ionic liquid and cocrystal multicomponent phases of lidocaine with azelaic acid by changing counterion ratios

Julija Zotova^a, Zaneta Wojnarowska^b, Brendan Twamley^c, Lidia Tajber^{a,*}

^a School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, College Green, Dublin 2, Ireland

^b Institute of Physics, University of Silesia, SMCEBI, 75 Pulku Piechoty 1A, 41-500 Chorzow, Poland

^c School of Chemistry, Trinity College Dublin, College Green, Dublin 2, Ireland

ARTICLE INFO

Article history:

Received 22 July 2021

Revised 28 September 2021

Accepted 29 September 2021

Available online 4 October 2021

Keywords:

Lidocaine

Azelaic acid

Cocrystal

Oligomeric ionic liquid

Thermal analysis

ABSTRACT

Tuning of physicochemical properties of ionic liquids and crystalline materials is a challenge that opens up unlimited possibilities for expanding applications and controlling biological activity of pharmaceutical multicomponent phases incorporating active pharmaceutical ingredients (APIs) with counterions or coformers. In this work we have investigated the effect of changing lidocaine (LID) and azelaic acid (AZE) ratios on the physicochemical properties of their corresponding multicomponent systems using a thermodynamics-based approach. Microscopy, X-ray diffraction analysis, infrared spectroscopy, nuclear magnetic resonance, and thermogravimetric analysis provided complementary characterisation. Mechanochemical synthesis of LID:AZE systems at a range of stoichiometries yielded at least two distinct liquid phases and two distinct crystalline phases, one of which involved a unique 2:3 LID:counterion composition not observed previously. Furthermore, to the best of our knowledge the formation of oligomeric ionic liquids involving dicarboxylic acids is also being reported for the first time. This work highlights the need for a careful characterisation of multicomponent systems, especially for pharmaceutical applications.

© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

A number of interesting works have been published very recently raising awareness on the continuum that exists between ionised and neutral pharmaceutical multicomponent systems [1–3]. A change in preparation methods, temperature or stoichiometry can modulate the ionic character of the system and yield different products as a result of complex interrelationship of kinetic and thermodynamic aspects [1,4–6]. In particular, there are examples illustrating that distinct crystalline structures obtained by varying stoichiometry of co-formers or counterions can tune the solid state properties and performance of an active pharmaceutical ingredient (API) [7–9].

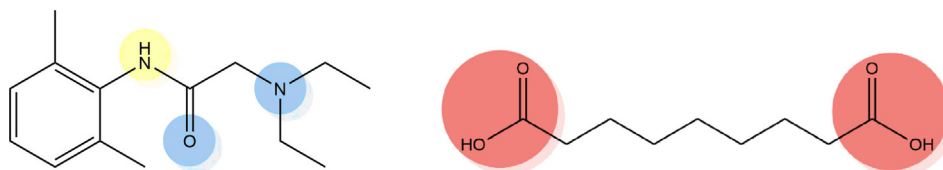
Although, the majority of the investigated pharmaceutically-relevant API multicomponent systems are crystalline the rising significance of low-melting point solids or even liquid forms of such systems has been recognised [10–15]. They include, but are not limited to ionic liquids, deep eutectic mixtures, ionic cocrystals

and oligomeric ionic liquids. Until recently, the intermolecular interactions that play the major role in the classification of the liquid forms were mainly considered at simple 1:1 stoichiometric ratios and stoichiometries dictated by the counterion of choice [16,17]. On the other hand, non-stoichiometric ratios were viewed as systems containing excess of either of the starting materials [18]. However, it has been shown that mixtures of the counterions or the co-formers at different stoichiometric ratios can potentially form distinct multicomponent systems not just in the solid but also in the liquid state [2,19].

Our previous work concentrated on a range of API-ILs incorporating lidocaine and medium-chain dicarboxylic acids as the counterions [20]. LID is an aminoamide drug used as a local anaesthetic with some antibacterial properties [21] and the molecule possesses one H-bond donor –NH group and 3H-bond acceptor groups (Scheme 1). LID is practically insoluble in water and is formulated as a salt to overcome the solubility constraints. The tertiary amine group has a pKa value of 7.9 rendering it a weak base and most of the known LID salts undergo ionisation at this site [22,23]. However, in an ionised form LID's membrane permeability is severely impeded [24]. Careful co-former or counterion selection for a

* Corresponding author.

E-mail address: ltajber@tcd.ie (L. Tajber).



Scheme 1. Molecular structures of LID (left) and AZE (right). Yellow- H-bond donor and acceptor; blue- H-bond acceptor; red- carboxylic acid groups.

new LID multicomponent phase formation can greatly improve the API's performance without undergoing chemical modification [14,25,26]. The LID ionic liquids (ILs) based on medium-chain dicarboxylic acids were evaluated in terms of their thermal and dynamic behaviour supported by crystallographic analysis in an attempt to devise a prediction tool for the structure–property relationship. Alternating trends in morphology, melting points, glass transition temperatures and crystallographic properties of the new phases were observed depending on the acid used [20].

In this work we have investigated the influence of changing stoichiometry of LID and azelaic acid (AZE), another medium-chain dicarboxylic acid on the physicochemical properties of their corresponding multicomponent systems using a thermodynamics-based approach, which includes the construction of the solid–liquid binary phase diagrams. Microscopy, X-ray diffraction analysis, infrared spectroscopy, nuclear magnetic resonance, and thermogravimetric analysis provide complimentary characterisation. The molecular structures of LID and the dicarboxylic acid investigated in the study are shown in Scheme 1. AZE is a dicarboxylic acid commonly used as a topical bactericidal, antioxidant and anti-inflammatory agent [27–29]. AZE is a weak acid with 2 carboxylic acid moieties at both ends of the alkyl chain with pK_a values of 4.550 and 5.498. The differences in pK_a values (i.e. $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$) are 3.35 and 2.4 meaning that both, salts and cocrystals could potentially be formed [30]. Other known LID:dicarboxylic acid multicomponent systems reported to date were solely ionized systems [20,23,31]. It was thus hypothesised that the LID:AZE combination would yield a similar LID:dicarboxylic acid system. However, mechanochemical synthesis of LID:AZE systems yielded at least two distinct liquid phases and two distinct solid phases, one of which involved a unique 2:3 LID:counterion composition not observed previously. Furthermore, to the best of our knowledge the formation of oligomeric ionic liquids involving dicarboxylic acids have been reported for the first time.

2. Materials and methods

2.1. Materials

LID (as a base) and azelaic acid (AZE) were purchased from Sigma-Aldrich (Ireland). Potassium bromide for Infrared analysis was obtained from Honeywell Fluka and was dried in a vacuum oven at room temperature prior to use. The purity of the compounds was at least 98%. All compounds were used as obtained. Absolute ethanol used was of HPLC grade (Fisher Scientific, UK).

2.2. Methods

2.2.1. Sample preparation

LID and AZE was processed at a range of molar fractions between 0.1:0.9 and 0.9:0.1 (LID:AZE). The constituents were accurately weighted with a Mettler Toledo MT5 microbalance (Mettler Toledo, Switzerland) and ground in an agate mortar and pestle until homogenous mixtures were obtained. A total of 200 mg of each sample was produced. A sample of each mixture was imme-

diately analysed and the remaining mixtures were transferred to 2 mL microcentrifuge tubes and kept at 4 °C until further analysis.

2.2.2. Polarised optical microscopy

Prior to analysis LID and AZE were recrystallised from ethanol. A small crystal of each, LID and AZE, were placed on a glass slide and were pushed together with the help of a needle. The glass slide was examined using Olympus BX53 polarising optical microscope (Ireland) equipped with a U-POT cross polarizer and a U-ANT analyser. Images were taken with an integrated Q IMAGING Fast 1394 camera (Olympus, Japan). The experiment was performed at room temperature [20].

2.2.3. Thermogravimetric analysis (TGA)

TGA was performed using Mettler TG50 measuring module coupled to a Mettler Toledo MT5 balance (Switzerland). Samples were weighed into an open aluminium pan (sample size approximately 5–11 mg) and heated from 25 °C to 200 °C at a rate of 10 K min^{−1} under nitrogen as a purge gas. Upon completion the samples were visually inspected and the thermograms were analysed for degradation using Mettler Toledo STARe software (version 6.10).

2.2.4. Differential scanning calorimetry (DSC)

DSC measurements were carried out using a PerkinElmer Pyris1 Diamond DSC unit (USA). The unit was refrigerated using a ULSP B. V. 130 cooling system (Netherlands) [20,32]. Approximately 3–6 mg samples were weighed into aluminium pans and sealed. The samples were heated from 25 °C to 115 °C at the rate of 10 K min^{−1} with nitrogen at a flow rate of 40 mL min^{−1} used as the purge gas. The samples were then supercooled to −60 °C at 300 K min^{−1} cooling rate and a second heating cycle was performed. Thermograms were analysed using Perkin Elmer Pyris software.

2.2.5. Fourier-transform infrared (FTIR) analysis

Prior to analysis LID:AZE mixtures at selected compositions were heated at 60 °C under nitrogen gas for 30 min to remove moisture. The samples were prepared as KBr disks using direct compression using a hydraulic press. Sample loading was approximately 1% (w/w). Infrared spectra were recorded on Spectrum One spectrometer (Perkin Elmer, USA). A spectral range of 650–4000 cm^{−1} and accumulation of 8 scans were used. Spectra was analysed using Spectrum v. 5.0.1 software.

2.2.6. Powder X-ray diffraction (PXRD) analysis

The LID:AZE samples were prepared at room temperature and were kept at 4 °C prior to analysis. PXRD was carried out at room temperature using Rigaku Miniflex II X-ray diffractometer (Japan) equipped with Cu K α radiation (1.54 Å) X-ray source. The samples were scanned over a 2 θ degrees range of 2–40° with a scan rate of 0.05°/s. The tube voltage and tube current used were 30 kV and 15 mA, respectively [20].

2.2.7. Single crystal X-ray diffraction (SXRD)

Preparation of Phase 1 (2:1 LID:AZE cocrystal) – A sample of LID:AZE at equimolar composition was heated until freely flowing liq-

uid was obtained. The liquid sample was poured inside an NMR tube and was kept in the fridge until crystals were observed.

Preparation of Phase 2 (2:3 LID:AZE ionic liquid) - Solidified polycrystalline powder at 1:1 M composition was obtained upon prolonged storage for 6 months at room temperature. A few crystals were removed with a needle to be seeded onto a drop of liquefied 1:2 LID:AZE mixture on a glass slide and kept at room temperature. Larger crystals of satisfactory quality for SXRD analysis were harvested after a week.

Data for 2:1 LID:AZE cocrystal and 2:3 LID:AZE salt samples were collected on a Bruker Apex Kappa Duo using Cu K α radiation ($\lambda = 1.54178$ Å) using a MiTeGen microloop and at 100(2) K (Oxford Cobra Cryosystem). Bruker APEX [33] software was used to collect, correct (Lorentz and polarization) and reduce data. Absorption corrections were applied using SADABS [34]. The structure was solved with the SHELXT [35] structure solution program using Intrinsic Phasing and refined with the SHELXL [36] refinement package using Least Squares minimisation with Olex2 [37], using the space group P2₁, with Z = 2 for the formula unit, C₃₇H₆₀N₄O₆. Details of the data and refinement are given in Table S1. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters; donor hydrogen atoms (H9a, H9b, 18, H30) were located and refined with restraints (DFIX). The absolute configuration was determined and confirmed by refining the Flack parameter as 0.3(2). CCDC 2098381 (Phase 1) and 2098382 (Phase 2) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. The pXRD and SXRD were compared using EXPO2014 [38] with a final Le Bail refinement using the Pearson VII peak shape function with a $w = 1.0/\text{count}$ weighting scheme. Final agreement factors, 2:1 LID:AZE cocrystal : $R_p = 10.017$, $R_{wp} = 14.605$, $R_e = 4.926$ and $\chi^2 = 8.791$; 2:3 LID:AZE salt : $R_p = 7.525$, $R_{wp} = 10.284$, $R_e = 6.203$, $\chi^2 = 2.748$.

2.2.8. Proton nuclear magnetic resonance (¹H NMR)

Crystalline 1:1 LID:AZE sample obtained upon prolonged storage at room temperature and 2:1 LID:AZE sample freshly prepared by neat grinding were dissolved in DMSO *d*₆. ¹H NMR measurements were performed using Bruker Avance III 400 MHz spectrometer. The NMR spectra were analysed using TopSpin 4.0.9 software. See SI and Fig. S1 for the ¹H NMR peak assignment.

3. Results and discussion

3.1. Morphology of samples

The study was initiated by solvent-free neat grinding mechanochemical synthesis of the LID:AZE systems at 0.1:0.9 – 0.9:0.1 M compositions. Samples in the $\chi_{\text{LID}} = 0.33$ to 0.66 range yielded semiliquid or soft solid (paste) samples at room temperature (Fig. 1a). On the contrary, systems at extreme molar LID or AZE molar fractions were solid powders. POM analysis was performed to visually examine the process of liquefaction. The POM images in Fig. 1b display the solid fusion experiment where recrystallised LID and AZE were placed side by side and solid state reactivity was observed. Crystalline regions that were in a direct contact started undergoing liquefaction at room temperature almost immediately and a noticeable change was observed at $t = 10$ min. At $t = 7$ days the entire interface has liquefied. This observation indicates that the melting point of the product of the solid-state reaction is below room temperature and such behaviour is characteristic of a liquid, or a “deep”, eutectic formation [20,39,40]. The remaining crystalline material that was not in a

direct contact has not been altered signifying the liquid eutectic does not diffuse nor dissolve parent materials further. POM image in Fig. 1c obtained at $t = 14$ days displays the formation of new dendritic structures. These structures may suggest an irregular eutectic morphology of this phase and/or a new phase formation [41]. Previously, POM demonstrated that LID reacted with glutaric acid or pimelic acid showed a similar behaviour and these LID:dicarboxylic acid mixtures underwent solid interdiffusion, while LID and suberic acid displayed true solid-state reactivity with the formation of a solid eutectic at the interface [20].

3.2. Thermal analysis

Starting materials LID and AZE as well as their mixtures at three different molar compositions (2:1, 1:1 and 1:2 LID:AZE) were analysed for thermal degradation by TGA (Fig. 2a). The results showed that the weight loss upon heating up to 120 °C did not exceed 2%, see Fig. 2b and c. Heating of the materials up to 120 °C generally results in dehydration or solvent evaporation. A very slight increase in weight loss exhibited by the binary mixtures might be associated with increased hygroscopicity of the samples following mixing. This observation is not unusual as it has been shown that low melting systems generally display elevated hygroscopicity [13]. On the other hand, upon heating to 200 °C the % weight loss is mainly caused by sample degradation. In this case LID and 2:1 LID:AZE underwent extensive degradation. However, upon addition of increased amount of AZE the degradation was decreased. These results are also illustrated by the sample colour change after the analysis. As seen in Fig. 2a 2:1 LID:AZE mixture turned very dark brown as compared to lighter brown colours of 1:1 and 1:2 samples.

DSC analysis of freshly prepared samples was carried out to study the phase change behaviour of the LID:AZE systems at various molar compositions. Fig. 3a presents a stack of DSC thermograms of the first heating cycle at different LID:AZE molar compositions. LID and AZE exhibit sharp endothermic peaks corresponding to their melting points of 69 °C and 106 °C, respectively. The melting point depression of LID is observed and is indicated by a blue arrow as increasing molar concentrations of AZE are added to the binary mixtures. A similar melting point depression is observed in AZE (indicated by a brown arrow) with increasing LID content. This observation follows simple binary phase behaviour as a result of decreasing purity of the starting components and has been observed in numerous multicomponent systems previously [42,43]. In addition to the endothermic peaks corresponding to the fusion events of the starting components the presence of new endothermic peaks in LID:AZE mixtures indicates the formation of new crystalline arrangements. As visible from the endothermic peaks in the yellow box the mechanochemical grinding of LID and AZE at high LID molar concentrations leads to a new phase formation, referred to as Phase 1. At $\chi_{\text{LID}} = 0.6$ and 0.55 a melting point depression of this Phase 1 is observed. The evolution of a double peak unique to 1:1 M composition infers the coexistence of two distinct crystalline arrangements. However, the second peak is not easily discerned in samples with higher AZE content, probably due to the creation of additional hydrogen bonds between the new crystalline structure and free diacid which leads to further sample liquefaction. This phenomenon has been described previously in the formation of deep eutectic mixtures (DEMs) and oligomeric ionic liquids [44,45]. It has been shown, but not generally recognised, that other forms of ionic liquids and DEMs can form at non-stoichiometric compositions and it is not just a 1:1 ionic liquid with excess carboxylic acid [19,46–48]. It has been proposed that such arrangement in the liquid phase can be described as $[\text{BH}^+][(\text{RCOO})_2\text{H}^-]$ [18]. The inherent slow crystallisation kinetics of these systems hinders phase identification. In an attempt to cur-

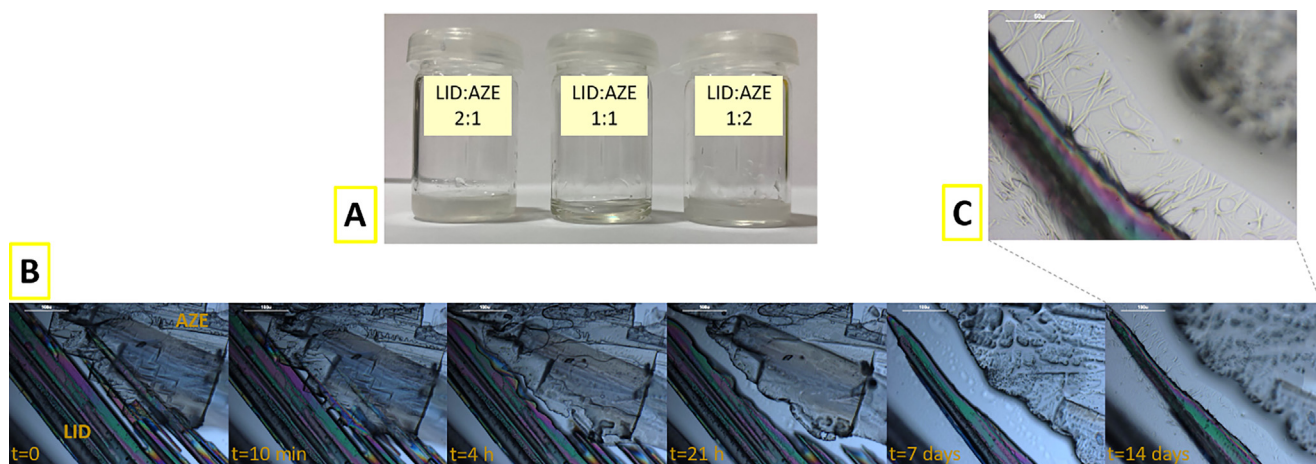


Fig. 1. A: Photographs of the LID:AZE samples immediately upon grinding. B: POM images of the solid fusion experiment. C: Interphase at a greater magnification showing dendritic formations.

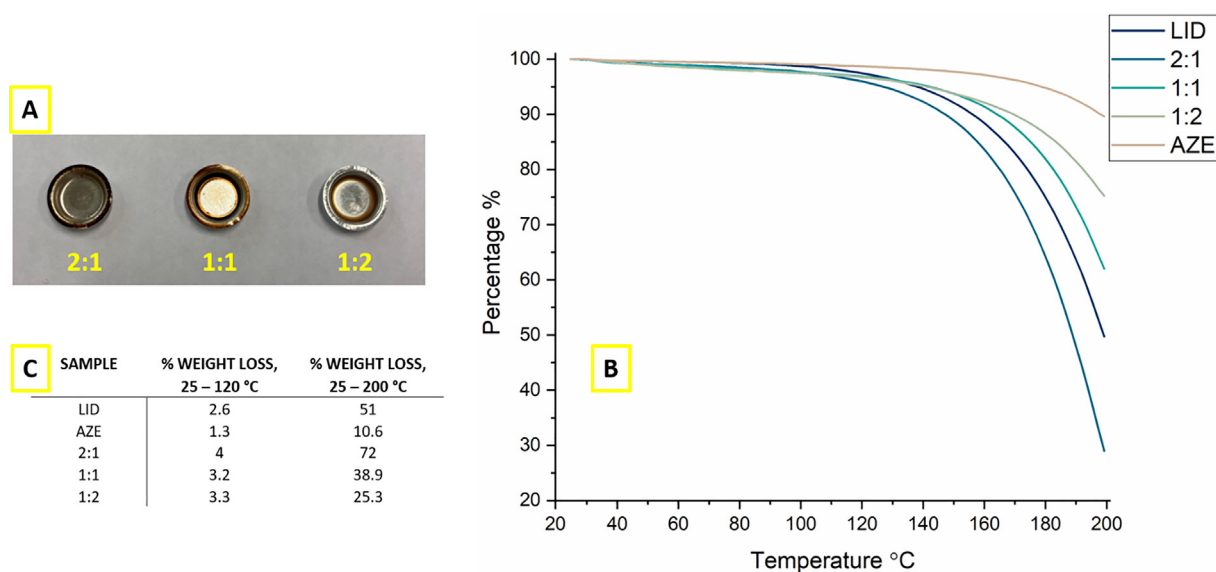


Fig. 2. A: Photographs of the TGA pans after analysis. B: TGA degradation profiles of LID, AZE and freshly ground binary mixtures. C: Values of % weight loss of LID, AZE and freshly ground binary mixtures upon heating up to 120 and 200 °C.

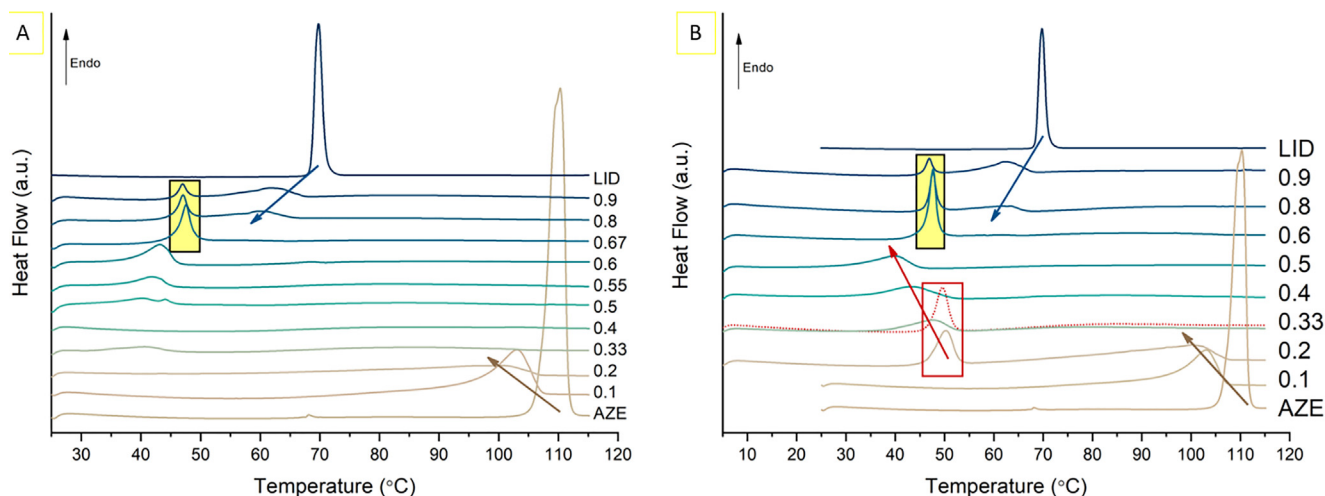


Fig. 3. A – First heating DSC thermograms of the samples prepared at room temperature; B – additional first heating DSC thermograms of the samples prepared at 4 °C. The red dotted line indicates a sample prepared at room temperature and cooled at 4 °C.

tail liquefaction samples in the range of $\chi_{\text{LID}} = 0.9$ to 0.2 were prepared and stored in the fridge for 1 day prior to analysis. As indicated by a red box and arrow in Fig. 3b, this sample treatment method enhanced new phase crystallisation, referred to as Phase 2.

Experimental T_m values were plotted as a function of LID molar fraction as seen in Fig. 4. Dashed lines represent theoretical Schroeder van Laar solubility curves calculated using Eq. (1), where T_{fus} (K) denotes the temperature of fusion and ΔH_{fus} (J mol⁻¹) denotes the enthalpy of fusion of the pure starting component, χ is the mole fraction of the pure starting component at a specified temperature T (K), and R is the gas constant.

$$T = \left(\frac{1}{T_{fus}} - \frac{R \ln \chi}{\Delta H_{fus}} \right) \quad (1)$$

It is evident that the melting points of the parent components can be reasonably predicted at their corresponding extreme molar fractions. This agreement suggests that the unreacted starting components remain in the mixture in their unchanged form and no additional intermolecular interactions are depressing their corresponding T_m . However, the T_m of the parent components disappear at 0.3:0.7–0.6:0.4 LID:AZE molar compositions. This region is highlighted in Fig. 4. This observation suggests new intermolecular interactions being created within the system and is corroborated by the appearance of melting events of Phase 1 and Phase 2. It is interesting to note that at the equimolar composition the melting events of these phases merge, thus creating a sensitive equilibrium where the identity of phase formation depends on fine sample preparation and storage variables.

Upon completion of the first heating step the samples at the entire range of compositions were fast cooled at a nominal rate of 300 K/min and then subjected to a second heating step. Fig. S2 presents a stack of second heating DSC thermograms which reveal the presence of glass transition events (T_g) in LID:AZE mixtures which implies the ability of the systems to be supercooled. Pure starting components do not exhibit T_g transitions as they crystallise during the cooling step. It is important to note that the samples at the extreme LID and AZE compositions also undergo partial crystallisation upon cooling and the T_g values of these systems are indicated by open star symbols in Fig. 4. As can be seen from Fig. 4,

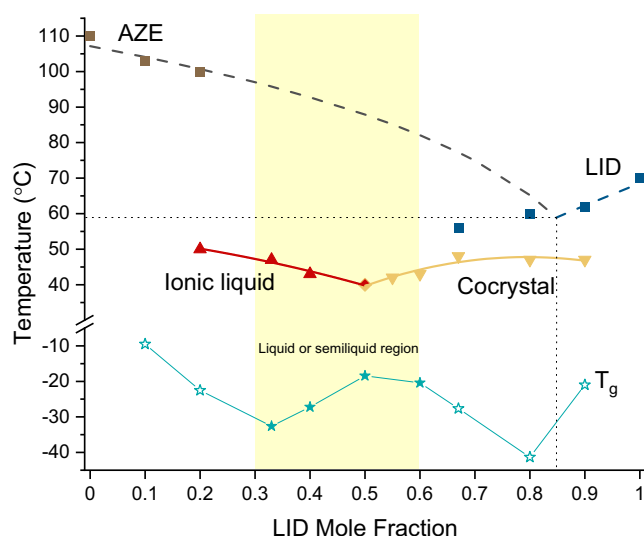


Fig. 4. Thermodynamic phase diagram, where T_m of Phase 1 (cocrystal) were obtained from samples prepared at room temperature, while T_m of Phase 2 (ionic liquid) were obtained from samples prepared at 4 °C. Dashed lines represent theoretical Schroeder van Laar solubility lines. Black dotted lines indicate theoretical eutectic composition and T_m . Open star symbols indicate T_g values of the samples that have undergone crystallisation on cooling.

there is a clear maximum in T_g at the equimolar composition of the acid and the base. The observed extremum in T_g behaviour can be explained in terms of ionicity degree. Previously, a marked increase in T_g has been correlated with the conversion of a given API into its corresponding salt form e.g. hydrochloride, sulphate or phosphate [44,49]. Moreover, it has been established that an increase in the T_g and melting point of classical aprotic ionic liquids is observed when the electrostatic interactions start to dominate van der Waals forces [50]. Consequently, it is expected that the supercooled equimolar LID:AZE system exhibits the most efficient proton transfer and thus, comprises the highest concentration of ionised species.

3.3. Investigation of ionicity in the supercooled state

FTIR spectroscopy was employed to investigate the changes in intermolecular interactions within the liquid systems as a function of LID:AZE molar composition (Fig. 5a) to corroborate the results obtained by thermal analysis. The systems were melted and analysed by FTIR immediately to mimic the supercooled state investigated by the second DSC heating cycle. The clear T_g maximum observed at the equimolar LID:AZE composition suggests the highest degree of ionisation and thus, ionic liquid formation. One of the most prominent peaks observed corresponds to the carbonyl stretching vibration and appears at 1664 cm⁻¹ and 1694 cm⁻¹ in LID and AZE spectra, respectively. The magnified carbonyl region is presented as an inset in Fig. 5b for clearer visualisation. However, spectra obtained for the binary LID:AZE mixtures exhibit an additional carbonyl signal not attributable to parent materials. This phenomenon is most clearly visible in the mixtures with higher LID content. In the 2:1 LID:AZE supercooled sample the signal is found at 1717 cm⁻¹ and its position is shifted to 1724 cm⁻¹ in 1:1 supercooled LID:AZE mixture. In $\chi_{\text{LID}} = 0.4$ mixture the peak appears as a shoulder at around 1717 cm⁻¹. The emergence of this peak may imply the formation of intermolecular H-bonds between the -NH moiety of the LID's amide group and the carbonyl group of the AZE. As a result of -NH group participating in the creation the new H-bond, the C=O bond is strengthened and a shift to higher wavenumbers is observed. The greatest shift at the 1:1 composition suggests the strongest amide-carbonyl H-bond formation, most probably due to formation of the homogenous 1:1 molecular arrangement. This reasoning is corroborated by the complete disappearance of pure LID signal as a result of being entirely used up in the 1:1 complex formation. Hence, giving rise to the observed T_g maximum. On the other hand, AZE C=O signal persists in the spectrum, which can be explained by the availability of 2 carbonyl groups and 1 being left unchanged. In addition, a prominent symmetric stretching carboxylate ion peak at 1540 cm⁻¹ appears in the spectra of mixtures, which provides an indication that ionisation in the form of proton transfer between LID and AZE has taken place.

The decreased intensity and wavenumber of the amide N-H stretch at 3250–3170 cm⁻¹ region is caused by the dilution of LID in AZE and the formation of the H-bond (*vide supra*). A peak assignment table is presented in Table S2. The presence of proton transfer in the 1:1 complex implies the formation of an ionic liquid. The systems with the higher acid content, i.e. in the range $\chi_{\text{LID}} = 0.4$ to 0.33 possess a greater number of hydrogen bonds formed within the complexes and, as a result, the systems are further liquefied. Depending on the arrangement of these additional H-bonds formed the compositions may be classified as either oligomeric ionic liquids or deep eutectic mixtures.

3.4. Investigation of crystalline phases

PXRD analysis of the samples prepared as described in Section 2.2.1 revealed the formation of a new crystalline phase at

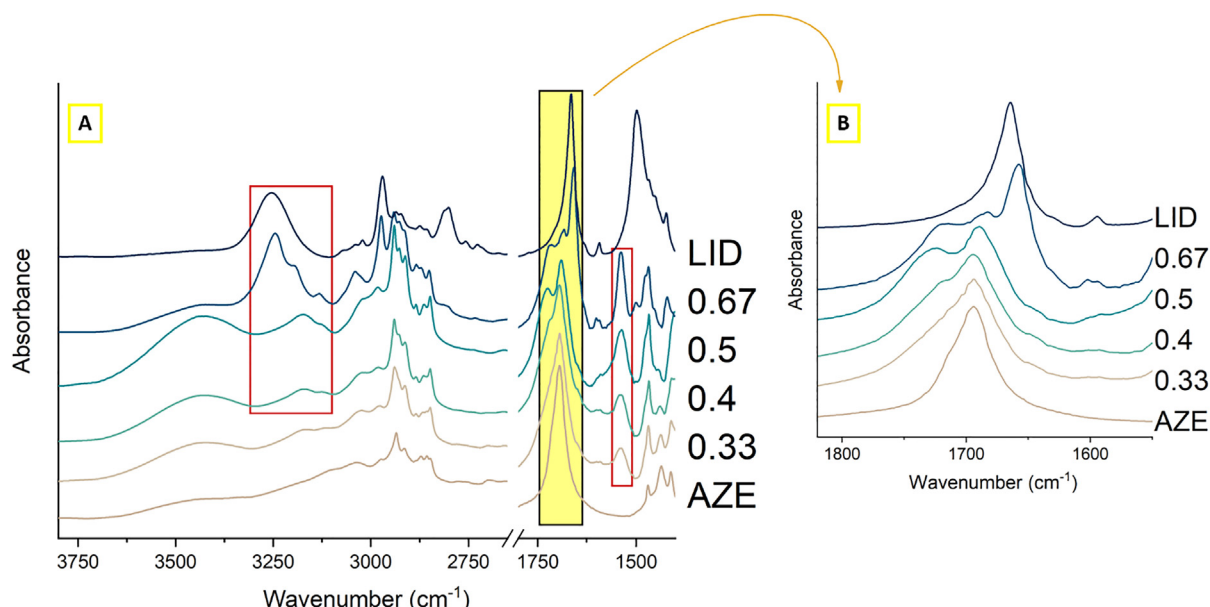


Fig. 5. A: FTIR spectra of the LID/AZE systems at various molar compositions. B: Inset with magnified carbonyl region of the LID/AZE systems.

$\chi_{\text{LID}} = 0.5$ to 0.2 range of compositions, as seen in Fig. 6. Melting of this new system, Phase 2, was first observed by thermal analysis (Fig. 4). The PXRD pattern corresponding to the new phase displays peaks that do not appear in the patterns on the parent materials, such as at $2\theta = 6^\circ, 11^\circ, 14^\circ$ and 16° . Low intensities of the peaks were observed due to the sample being partially liquid. A peak at $2\theta = 6^\circ$ appears at a lower position as compared to the first peaks of the parent materials signifying the formation of a larger crystal lattice.

An attempt to obtain a single crystal of Phase 2 has unexpectedly resulted in an identification of a second, new crystalline phase, Phase 1. The PXRD pattern of this system is highlighted in red colour in Fig. 6 and appears to be very similar to pure LID with some differences. In particular, the 2:1 system displays a peak at $2\theta = 8.4^\circ$ as compared to a peak at $2\theta = 8.2^\circ$ seen in LID, and displays unique peaks at $2\theta = 11^\circ, 18^\circ, 24^\circ, 27^\circ$ and 28° . These peaks are also visible in the pattern of the $\chi_{\text{LID}} = 0.5$ mixture implying sample heterogeneity, where both new crystalline products coexist in equilibrium.

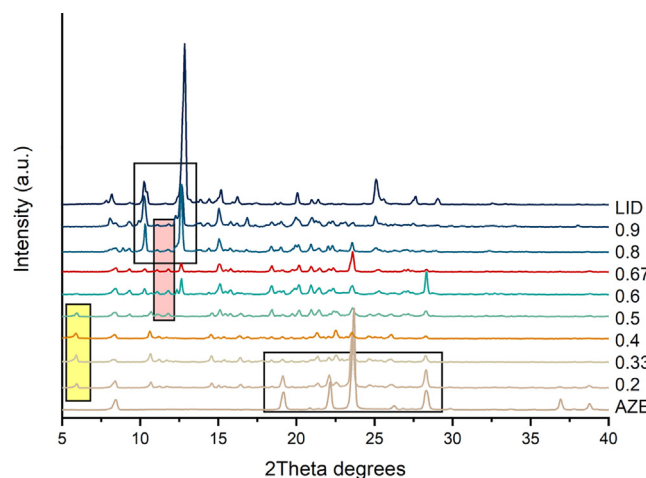


Fig. 6. A stack of PXRD traces at the range of LID molar fractions χ_{LID} . The pattern highlighted in red corresponds to Phase 1 and the pattern highlighted in orange corresponds to Phase 2.

3.5. Effects of sample preparation and storage on systems speciation

It is important to note the impact of method of sample preparation and storage conditions on the LID/AZE complex formation. DSC analysis was performed using freshly ground samples without preheating in order to capture any thermal transitions that occur at lower temperatures. For example, a freshly ground 1:1 LID/AZE sample appears as a liquid (Fig. 1a) with a small amount of solid particles suspended within the liquid matrix. These particles were later identified as nucleation sites for the formation of the new crystalline complexes (Phase 2) and DSC thermograms of these samples allowed to capture their melting points. However, preheating 1:1 LID/AZE samples up to 60°C in an oven destroyed these crystallisation nucleation sites resulting in a stable for at least 6 months ionic liquid that did not crystallise on storage at room temperature. PXRD analysis of the freshly ground samples allowed identification of the new crystalline structures being formed from these nucleation sites, these crystals showed distinct PXRD patterns as seen in Fig. 6. PXRD analysis of the equimolar sample performed after preheating did not display any diffraction peaks and resulted in a disordered “halo”. The samples with the higher AZE content exhibited analogous behaviour. Therefore, it is possible to conclude that LID/AZE molten mixtures form distinct ionic liquid phases at a range of equimolar and non-stoichiometric ratios with greater acid content.

On the other hand, the base-rich 2:1 LID/AZE mixture was not as sensitive to environmental variables. Crystalline Phase 1 was successfully obtained by both methods, neat grinding at room temperature and co-melting parent components in an oven. Another important observation to note is the equilibrium of the 2:1 and 1:1 complex formation in the LID/AZE equimolar mixtures. Depending on the preparation and storage conditions different crystalline phases were observed and the summary of the observations is presented in Table 1. The bulk synthesis of Phase 2 was not successful. A range of seeding experiments were also attempted, where a polycrystalline impure Phase 2 was seeded in a molten equimolar LID/AZE mixture, in a molten 1:2 LID/AZE mixture and in multiple organic solvents. The impure Phase 2 contained a mixture of crystalline LID and both of the crystalline systems. As a result, in most cases an identical impure polycrystalline material was obtained. These results can be explained by the differences

Table 1
Impact of preparation and storage variables on phase crystallisation in equimolar LID:AZE mixtures.

Storage	Preparation				
	Neat grinding, RT	Neat grinding, 4 °C	Co-melting at 60 °C	Seeding in molten 1:1 mixture	Seeding in molten 1:2 mixture
At RT	Impure polycrystalline	Not performed	Liquid	Impure polycrystalline	Phase 2
At 4 °C	Impure polycrystalline	Impure polycrystalline*	Liquid**	Not performed	Not performed
Under vacuum	Phase 1	Not performed	Phase 1	Impure polycrystalline	Not performed

* Phase 2 was only identified upon prolonged storage (about 3–6 months after sample preparation).

** Only once has this sample crystallised as Phase 2 in an NMR tube and this sample was used for SXRD analysis.

in the stability and solubility exhibited by these complexes, where the least soluble and most stable system crystallising out first. This phenomenon has been identified and investigated in other binary systems with LID [51] and other APIs [1,52,53]. However, seeding in a molten acid-rich 1:2 mixture yielded a pure Phase 1 crystal with quality satisfactory for SXRD analysis. The crystallisation work performed with LID:AZE mixtures was very challenging and before single crystals were obtained a suspicion was raised that one of the crystalline phases might actually be a degradation product. To check for sample degradation ^1H NMR analysis was performed. The peak assignment presented in Fig. S1 indicates that Phase 1 and Phase 2 differ in the solid state, but degradation products were not observed in the ^1H NMR spectra.

3.6. Single crystal XRD analysis

Single crystals of the two distinct crystalline phases, Phase 1 and Phase 2, were obtained and analysed. Phase 1, the 2:1 LID:AZE complex with a melting point of 47 °C and crystallising in a monoclinic $P2_1$ space group was identified as a cocrystal. The theoretical PXRD pattern generated from the SXRD data closely matched experimental PXRD patterns by visual inspection and a Le Bail refinement with difference pattern shown in Fig. S3. The asymmetric unit contains 2 LID molecules and 1 AZE molecule held together by H-bonding interactions as seen in Fig. 7a. The strongest H-bonds are formed between the LID tertiary amine moiety and both AZE carboxylic groups with $d(\text{D}\cdots\text{A}) = 2.583(3)$ and 2.603

(3) Å. The formation of a cocrystal, rather than a salt is also evidenced by the AZE carboxylic C—O bond length analysis. In salts, the deprotonation of a carboxylic acid results in a carboxylate ion possessing two C—O bonds with similar $D_{\text{C-O}}$, i.e. the $\Delta D_{\text{C-O}} < 0.03$ Å, where $\Delta D_{\text{C-O}}$ is the difference in length between the two C—O bonds within a carboxylate moiety. In cocrystals, neutral carboxylic acids would possess two distinct C—O bonds with $\Delta D_{\text{C-O}} > 0.08$ Å [54]. The 2:1 LID:AZE complex exhibits high $\Delta D_{\text{C-O}}$ values of 0.119 and 0.125 Å confirming cocrystal formation. The crystal structure is further stabilised by the hydrogen-bonded $\text{NH}\cdots\text{O}$ heterosynthons ($d(\text{D}\cdots\text{A}) = 2.900(3)$ and $2.932(3)$ Å) formed between the LID amide moieties and further weak $\text{CH}\cdots\text{O}$ interactions ($d(\text{D}\cdots\text{A}) = 3.243(3)$ Å). The resulting structure forms zig-zag crystallisation patterns as seen in Fig. 7b. See Fig. S5 and Table S3 for atom labels and a list of all hydrogen bonds present within the system.

Interestingly, despite the fact that the crystalline 2:1 LID:AZE system is a cocrystal, FTIR analysis showed that the carboxylate ion peak was also visible in the supercooled mixture of the same composition (Fig. 5). This is due to the ability of the system to be partially liquified as indicated by the presence of a T_g transition observed by DSC (Fig. 4). Hence, the supercooled fraction of the sample exhibits proton transfer due to increased molecular mobility.

The second crystalline phase, Phase 2, comprises a highly unusual 2:3 LID:AZE ratio and it is characterised by a melting point onset of 50 °C. No other crystalline structures involving LID at such

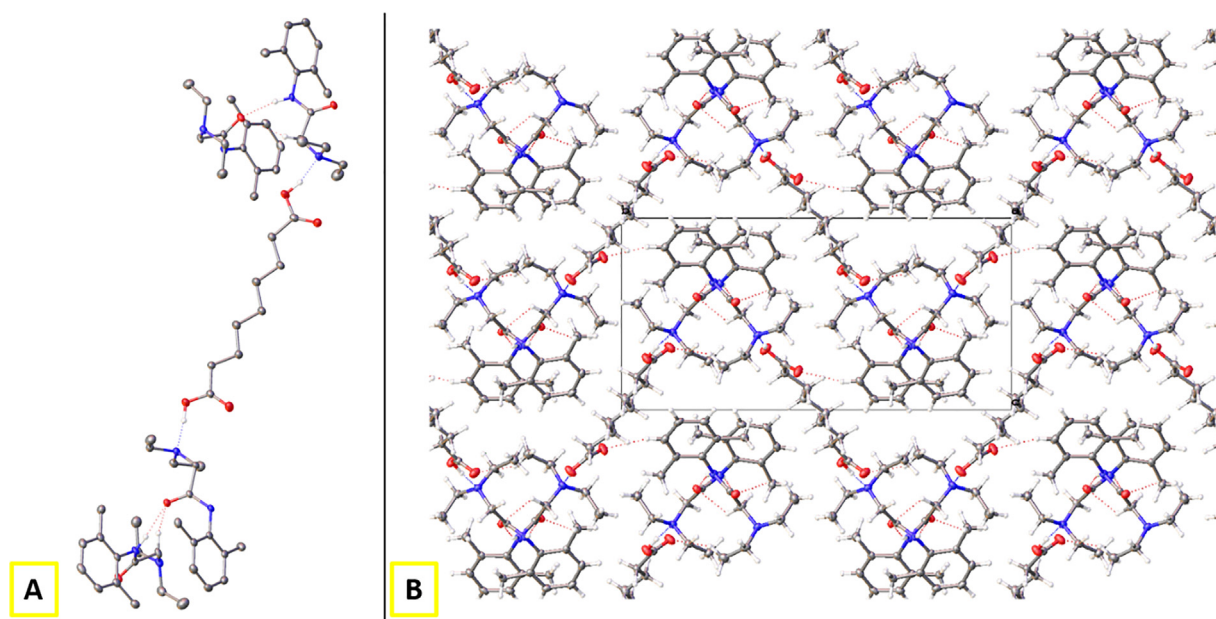


Fig. 7. A: Primary hydrogen bonding motif (dotted lines) in the 2:1 LID:AZE cocrystal (Phase 1). Displacement shown at 50% probability. Only hydrogen atoms involved in the H-bonding motif are shown. B: Packing diagram of 2:1 LID:AZE viewed normal to the a-axis. Dotted lines indicate hydrogen bonding interactions. Displacement shown at 50% probability.

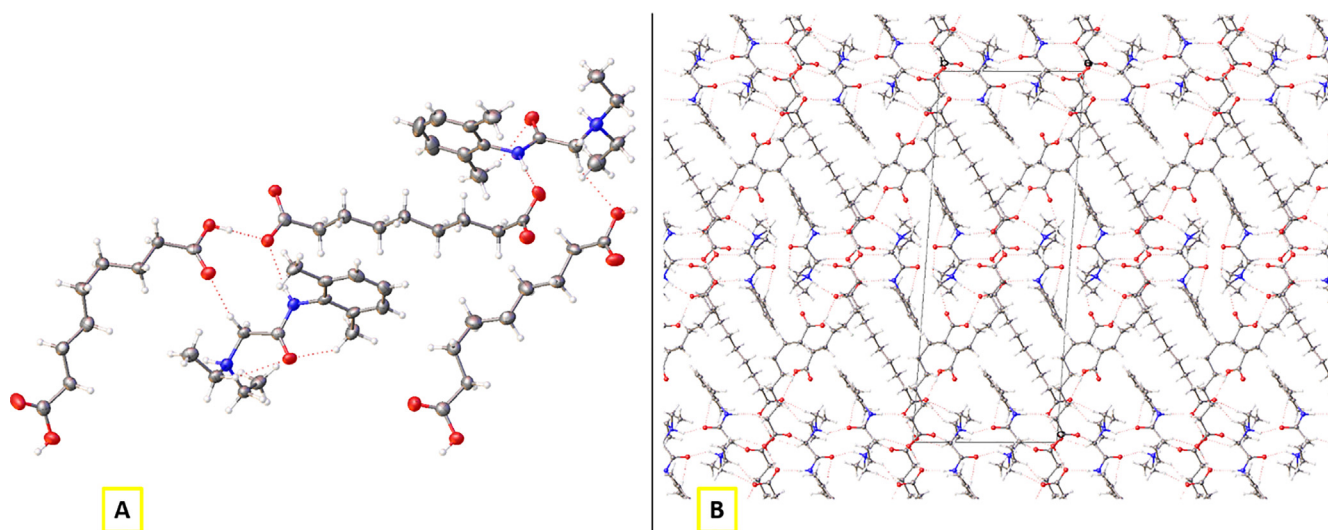


Fig. 8. **A:** Primary hydrogen bonding motif (dotted lines) in the 2:3 LID:AZE IL (Phase 2). Displacement shown at 50% probability. Only hydrogen atoms involved in the H-bonding motif are shown. **B:** Packing diagram of 2:3 LID:AZE viewed normal to the *a*-axis. Dotted lines indicate hydrogen bonding interactions. Displacement shown at 50% probability.

ratio with other counterions or co-formers has been deposited in the CSD database to date. The complex crystallises in a triclinic $P\bar{1}$ space group with 2 LID and 3 AZE molecules constituting an asymmetric unit. Theoretical PXRD patterns generated from the SXRD data closely match experimental PXRD patterns by visual inspection and a Le Bail refinement with difference pattern shown in Fig. S4. The crystalline structure is composed of 2 unionised AZE molecules, 1 doubly ionised AZE anion and 2 ionised LID cations which are held together via a complex network of hydrogen bonding interactions as seen in Fig. 8a-b. The 2 LID molecules are ionised at the tertiary amine sites via a proton transfer from both carboxyl moieties of a single AZE molecule. The complete deprotonation of AZE is supported by C–O bond analysis, where the two carboxyl moieties possess ΔD_{C-O} of 0.004 and 0.006 Å. The deprotonated carboxylate anions form hydrogen bonding interactions with $LIDH^+$ cations via all possible amine and amide H-bond donors, the strongest of which occurs between the carboxylate anion and an amide moiety $COO \cdots NH$ with $d(D \cdots A) = 2.811(6)$ Å. The doubly deprotonated AZE anion is further stabilised by H-bonds arising from unionised AZE carboxyl donors with $d(D \cdots A)$ distances ranging from 2.559(6) to 2.633(6) Å. See Fig. S6 and Table S4 for atom labels and a list of all hydrogen bonds present within the system. The structure is highly complex which explains the great difficulty faced during crystallisation efforts.

The molecular arrangement resembles the bonding pattern characteristic of oligomeric ionic liquids. However, all oligomeric ILs reported to date are formed from monocarboxylic acids and the generalised molecular formula is generally accepted as $[BH^+][RCOO_2H^-]$ [18]. The LID:AZE complex presented in this paper is the first example of oligomeric ionic liquid composed of anions derived from dicarboxylic acids. The molecular formula of the crystalline oligomeric complex may be written as $[(BH^+)_2][(HOOCRCOOH)_2(OOCCRCOO)^{2-}]$. Due to the presence of a greater number of H-bonding donors and resultant increased complexity of the potential ion patterns the molecular formula characterising this crystalline complex may or may not be applicable to other dimeric or higher order oligomeric anions and ionic liquids. It is also important to note that the crystalline structure corroborates the interactions in the solid state and these findings support the presence of analogous interactions in the liquid phase. Therefore, the 2:3 crystalline salt is the equivalent solid structure to the 2:3 oligomeric ionic liquid in the liquid phase. In this context, the

molecular formula of the 1:2 LID:AZE oligomeric ionic liquid is $[BH^+][[(HOOCRCOO)_2H^-]]$.

4. Conclusions

This work has highlighted the importance of considering a range of stoichiometric ratios for the formation of multicomponent systems incorporating acid-base pairs. Despite a series of equimolar LID:dicarboxylic acid salts published previously we have demonstrated that LID and AZE binary mixtures at various molar compositions can form a range of distinct multicomponent phases. This approach allows for fine-tuning of physicochemical and crystallisation properties of a binary system without altering its constituents. Neat grinding of LID and AZE has resulted in the formation of liquid or semiliquid systems at the $\chi_{LID} = 0.33$ – 0.67 M fractions, where 1:1 composition exhibited the highest ionicity attributable to an ionic liquid formation. The greatest extent of liquefaction at $\chi_{LID} = 0.4$ was attributed to an oligomeric ionic formation, the crystal structure of which was solved to be a 2:3 oligomeric crystalline ionic liquid. To the best of our knowledge, such system is the first example of an oligomeric ionic liquid composed of anions derived from dicarboxylic acids with a $[(BH^+)_2][(HOOCRCOOH)_2(OOCCRCOO)^{2-}]$ general molecular formula. In addition, a crystal structure of 2:1 LID:AZE cocrystal was also successfully obtained. These results suggest that prediction of acid-base multicomponent systems formation is more challenging when variable stoichiometric ratios are considered. However, addressing the non-stoichiometric approach allows for a better understanding, modification and visualisation of alternative forms of multicomponent phases.

CRediT authorship contribution statement

Julija Zotova: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Zaneta Wojnarowska:** Conceptualization, Methodology, Formal analysis, Investigation. **Brendan Twamley:** Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Visualization. **Lidia Tajber:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was funded by Science Foundation Ireland, grant number 15/CDA/3602 and supported by the European Cooperation on Science and Technology (COST) Action CA18112 “Mechanochemistry for Sustainable Industry”.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.molliq.2021.117737>.

References

- [1] D. Bernasconi, S. Bordignon, F. Rossi, E. Priola, C. Nervi, R. Gobetto, D. Voinovich, D. Hasa, N.T. Duong, Y. Nishiyama, M.R. Chierotti, Selective Synthesis of a Salt and a Cocrystal of the Ethionamide-Salicylic Acid System, *Cryst. Growth Des.* 20 (2) (2020) 906–915, <https://doi.org/10.1021/acs.cgd.9b01299>.
- [2] M.E. Easton, K. Li, H.M. Titi, S.P. Kelley, R.D. Rogers, Controlling the Interface between Salts, Solvates, Co-crystals, and Ionic Liquids with Non-stoichiometric Protic Azolium Azolates, *Cryst. Growth Des.* 20 (4) (2020) 2608–2616, <https://doi.org/10.1021/acs.cgd.9b01733>.
- [3] H. Lengauer, D. Makuc, D. Šterk, F. Perdih, A. Pichler, T.T. Lušin, J. Plavec, Z. Časar, Co-crystals, salts or mixtures of both? The case of tenofovir alafenamide fumarates, *Pharmaceutics* 12 (2020) 342, <https://doi.org/10.3390/pharmaceutics12040342>.
- [4] D. Wiechert, D. Mootz, Molecular beside ionic: Crystal structures of a 1/1 and a 1/4 adduct of pyridine and formic acid, *Angew. Chemie - Int. Ed.* 38 (1999) 1974–1976, [https://doi.org/10.1002/\(sici\)1521-3773\(19990712\)38:13/14<1974::aid-anie1974>3.0.co;2-f](https://doi.org/10.1002/(sici)1521-3773(19990712)38:13/14<1974::aid-anie1974>3.0.co;2-f).
- [5] S.R. Perumalla, C. Wang, Y. Guo, L. Shi, C.C. Sun, Robust bulk preparation and characterization of sulfamethazine and saccharine salt and cocrystal polymorphs, *CrystEngComm* 21 (13) (2019) 2089–2096, <https://doi.org/10.1039/C8CE01076E>.
- [6] P. Stainton, T. Grecu, J. McCabe, T. Munshi, E. Nauha, I.J. Scowen, N. Blagden, First Comparative Study of the Three Polymorphs of Bis(isonicotinamide) Citric Acid Cocrystals and the Concomitant Salt 4-Carbamoylpyridinium Citrate Isonicotinamide, *Cryst. Growth Des.* 18 (7) (2018) 4150–4159, <https://doi.org/10.1021/acs.cgd.8b00597>.
- [7] B. Saikia, P. Bora, R. Khatioda, B. Sarma, Hydrogen Bond Synthons in the Interplay of Solubility and Membrane Permeability/Diffusion in Variable Stoichiometry Drug Cocrystals, *Cryst. Growth Des.* 15 (11) (2015) 5593–5603, <https://doi.org/10.1021/acs.cgd.5b01293>.
- [8] Z.I. Li, A.J. Matzger, Influence of Coformer Stoichiometric Ratio on Pharmaceutical Cocrystal Dissolution: Three Cocrystals of Carbamazepine/4-Aminobenzoic Acid, *Mol. Pharm.* 13 (3) (2016) 990–995, <https://doi.org/10.1021/acs.molpharmaceut.5b00843>.
- [9] M. Samipillai, S. Rohani, The role of higher coformer stoichiometry ratio in pharmaceutical cocrystals for improving their solid-state properties: The cocrystals of progesterone and 4-hydroxybenzoic acid, *J. Cryst. Growth* 507 (2019) 270–282, <https://doi.org/10.1016/j.jcrysgro.2018.10.050>.
- [10] C. Agatemor, K.N. Ibsen, E.E.L. Tanner, S. Mitragotri, Ionic liquids for addressing unmet needs in healthcare, *Bioeng. Transl. Med.* 3 (1) (2018) 7–25, <https://doi.org/10.1002/btm2.10083>.
- [11] R. Ferraz, L.C. Branco, C. Prudêncio, J.P. Noronha, Ž. Petrovski, Ionic liquids as active pharmaceutical ingredients, *ChemMedChem* 6 (6) (2011) 975–985, <https://doi.org/10.1002/cmdc.201100082>.
- [12] J.L. Shamshina, P.S. Barber, R.D. Rogers, Ionic liquids in drug delivery, *Expert Opin. Drug Deliv.* 10 (10) (2013) 1367–1381, <https://doi.org/10.1517/17425247.2013.808185>.
- [13] A. Balk, U. Holzgrabe, L. Meinel, Pro et contra’ ionic liquid drugs - Challenges and opportunities for pharmaceutical translation, *Eur. J. Pharm. Biopharm.* 94 (2015) 291–304, <https://doi.org/10.1016/j.ejpb.2015.05.027>.
- [14] W.L. Hough, M. Smiglak, H. Rodríguez, R.P. Swatloski, S.K. Spear, D.T. Daly, J. Pernak, J.E. Grisel, R.D. Carliss, M.D. Soutullo, J.H. Davis Jr., R.D. Rogers, The third evolution of ionic liquids: active pharmaceutical ingredients, *New J. Chem.* 31 (2007) 1429, <https://doi.org/10.1039/b706677p>.
- [15] A. Umerska, K. Bialek, J. Zotova, M. Skotnicki, L. Tajber, Anticrystal engineering of ketoprofen and ester local anesthetics: Ionic liquids or deep eutectic mixtures?, *Pharmaceutics* 12 (2020) 368, <https://doi.org/10.3390/pharmaceutics12040368>.
- [16] B. Nuthakki, T.L. Greaves, I. Krodziewska, A. Weerawardena, M.I. Bugar, R.J. Mulder, C.J. Drummond, B. Nuthakki, T.L. Greaves, I. Krodziewska, A. Weerawardena, M.I. Bugar, R.J. Mulder, C.J. Drummond, Protic Ionic Liquids and Ionicity, *Aust. J. Chem.* 60 (2007) 21–28, <https://doi.org/10.1071/CH06363>.
- [17] W. Ogiwara, H. Kosukegawa, H. Ohno, Proton-conducting ionic liquids based upon multivalent anions and alkylimidazolium cations, *Chem. Commun.* (2006) 3637–3639, <https://doi.org/10.1039/B606186A>.
- [18] M.A.R. Martins, P.J. Carvalho, L.M.N.B.F. Santos, S.P. Pinho, J.A.P. Coutinho, The impact of oligomeric anions on the speciation of protic ionic liquids, *Fluid Phase Equilib.* 531 (2021) 112919, <https://doi.org/10.1016/j.fluid.2020.112919>.
- [19] K.M. Johansson, E.I. Izgorodina, M. Forsyth, D.R. Macfarlane, K.R. Seddon, Protic ionic liquids based on the dimeric and oligomeric anions: [(AcO)_xHx-1]⁻, *Phys. Chem. Chem. Phys.* 10 (2008) 2972–2978, <https://doi.org/10.1039/b801405a>.
- [20] J. Zotova, Z. Wojnarowska, B. Twamley, M. Paluch, L. Tajber, Green Synthesis of Lidocaine Ionic Liquids and Salts: Mechanisms of Formation and Interactions in the Crystalline and Supercooled States, *ACS Sustain. Chem. Eng.* 8 (49) (2020) 18266–18276, <https://doi.org/10.1021/acssuschemeng.0c06811>.
- [21] J. Sedef Gocmen, U. Buyukkocak, O. Caglayan, A. Aksoy, In vitro antibacterial effects of topical local anesthetics, *J. Dermatolog. Treat.* 19 (6) (2008) 351–353, <https://doi.org/10.1080/09546630802050498>.
- [22] G.A. Neville, Z.R. Regnier, Hydrogen bonding in lidocaine salts. I. The NH stretching band and its dependence on the associated anion, *Can. J. Chem.* 47 (1969) 4229–4235.
- [23] D. Braga, L. Chelazzi, F. Grepioni, E. Dichiarante, M.R. Chierotti, R. Gobetto, Molecular salts of anesthetic lidocaine with dicarboxylic acids: Solid-state properties and a combined structural and spectroscopic study, *Cryst. Growth Des.* 13 (6) (2013) 2564–2572, <https://doi.org/10.1021/cg400331h>.
- [24] R. Pérez-Isidoro, F.J. Sierra-Valdez, J.C. Ruiz-Suárez, Anesthetic Diffusion Through Lipid Membranes Depends on the Protonation Rate, *Sci. Rep.* 4 (2015) 7534, <https://doi.org/10.1038/srep07534>.
- [25] Y. Miwa, H. Hamamoto, T. Ishida, Lidocaine self-sacrificially improves the skin permeation of the acidic and poorly water-soluble drug etodolac via its transformation into an ionic liquid, *Eur. J. Pharm. Biopharm.* 102 (2016) 92–100, <https://doi.org/10.1016/j.ejpb.2016.03.003>.
- [26] P. Berton, K.R. Di Bona, D. Yancey, S.A.A. Rizvi, M. Gray, G. Gurau, J.L. Shamshina, J.F. Rasco, R.D. Rogers, Transdermal Bioavailability in Rats of Lidocaine in the Forms of Ionic Liquids, Salts, and Deep Eutectic, *ACS Med. Chem. Lett.* 8 (5) (2017) 498–503, <https://doi.org/10.1021/acsmmedchemlett.6b00504>.
- [27] A. Fitton, K.L. Goa, Azelaic Acid: A Review of its Pharmacological Properties and Therapeutic Efficacy in Acne and Hyperpigmentary Skin Disorders, *Drugs* 41 (5) (1991) 780–798, <https://doi.org/10.2165/00003495-199141050-00007>.
- [28] J.P. Leeming, K.T. Holland, R.A. Bojar, The in vitro antimicrobial effect of azelaic acid, *Br. J. Dermatol.* 115 (5) (1986) 551–556, <https://doi.org/10.1111/j.1365-2133.1986.tb05764.x>.
- [29] M.A. Sieber, J.K.E. Hegel, Azelaic acid: Properties and mode of action, *Skin Pharmacol. Physiol.* 27 (s1) (2014) 9–17, <https://doi.org/10.1159/000354888>.
- [30] J. Stoimenovski, E.I. Izgorodina, D.R. MacFarlane, Ionicity and proton transfer in protic ionic liquids, *Phys. Chem. Chem. Phys.* 12 (2010) 10341–10347, <https://doi.org/10.1039/c0cp00239a>.
- [31] Z. Wojnarowska, K.J. Paluch, E. Shofiet, C. Schick, L. Tajber, J. Knapik, P. Włodarczyk, K. Grzybowski, S. Hensel-Bielowska, S.P. Verevkin, M. Paluch, Molecular origin of enhanced proton conductivity in anhydrous ionic systems, *J. Am. Chem. Soc.* 137 (3) (2015) 1157–1164, <https://doi.org/10.1021/ja5103458>.
- [32] Z. Wojnarowska, W. Smolka, J. Zotova, J. Knapik-Kowalczyk, A. Sherif, L. Tajber, M. Paluch, The effect of electrostatic interactions on the formation of pharmaceutical eutectics, *Phys. Chem. Chem. Phys.* 20 (43) (2018) 27361–27367, <https://doi.org/10.1039/C8CP05905E>.
- [33] Bruker, APEX, 2012.
- [34] Bruker, SADABS, 2001.
- [35] G.M. Sheldrick, Foundations and Advances SHELXT-Integrated space-group and crystal-structure determination, *Acta Cryst. A* 71 (2015) 3–8, <https://doi.org/10.1107/S2053273314026370>.
- [36] G.M. Sheldrick, Crystal structure refinement with SHELXL, *Acta Crystallogr. Sect. C Struct. Chem.* C 71 (2015) 3–8, <https://doi.org/10.1107/S2053229614024218>.
- [37] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, OLEX2: A complete structure solution, refinement and analysis program, *J. Appl. Crystallogr.* 42 (2) (2009) 339–341, <https://doi.org/10.1107/S0021889808042726>.
- [38] A. Altomare, C. Cuocci, C. Giacovazzo, A. Moliterni, R. Rizzi, N. Corriero, A. Falcicchio, EXPO2013: A kit of tools for phasing crystal structures from powder data, *J. Appl. Crystallogr.* 46 (4) (2013) 1231–1235, <https://doi.org/10.1107/S0021889813013113>.
- [39] A.P. Abbott, G. Capper, D.L. Davies, R.K. Rasheed, V. Tambyrajah, Novel solvent properties of choline chloride/urea mixtures, *Chem. Commun.* (2003) 70–71, <https://doi.org/10.1039/B210714G>.
- [40] M.A.R. Martins, S.P. Pinho, J.A.P. Coutinho, Insights into the Nature of Eutectic and Deep Eutectic Mixtures, *J. Solution Chem.* 48 (7) (2019) 962–982, <https://doi.org/10.1007/s10953-018-0793-1>.

- [41] W. Kurz, D.J. Fisher, Dendrite growth in eutectic alloys: the coupled zone, *Int. Met. Rev.* 24 (1) (1979) 177–204, <https://doi.org/10.1179/imtr.1979.24.1.177>.
- [42] G. Annat, M. Forsyth, D.R. MacFarlane, Ionic liquid mixtures-variations in physical properties and their origins in molecular structure, *J. Phys. Chem. B.* 116 (28) (2012) 8251–8258, <https://doi.org/10.1021/jp3012602>.
- [43] G.J. Maximo, R.J.B.N. Santos, P. Brandão, J.M.S.S. Esperança, M.C. Costa, A.J.A. Meirelles, M.G. Freire, J.A.P. Coutinho, Generating ionic liquids from ionic solids: An investigation of the melting behavior of binary mixtures of ionic liquids, *Cryst. Growth Des.* 14 (9) (2014) 4270–4277, <https://doi.org/10.1021/cg500655s>.
- [44] J. Stojmenovski, P.M. Dean, E.I. Izgorodina, D.R. MacFarlane, Protic pharmaceutical ionic liquids and solids: Aspects of protonics, *Faraday Discuss.* 154 (2012) 335–352, <https://doi.org/10.1039/C1FD00071C>.
- [45] K. Bica, J. Shamshina, W.L. Hough, D.R. MacFarlane, R.D. Rogers, Liquid forms of pharmaceutical co-crystals: exploring the boundaries of salt formation, *Chem. Commun.* 47 (8) (2011) 2267–2269, <https://doi.org/10.1039/C0CC04485G>.
- [46] S.P. Kelley, A. Narita, J.D. Holbrey, K.D. Green, W.M. Reichert, R.D. Rogers, Understanding the effects of ionicity in salts, solvates, co-crystals, ionic co-crystals, and ionic liquids, rather than nomenclature, is critical to understanding their behavior, *Cryst. Growth Des.* 13 (3) (2013) 965–975, <https://doi.org/10.1021/cg4000439>.
- [47] P. Berton, S.P. Kelley, H. Wang, A.S. Myerson, R.D. Rogers, Separate mechanisms of ion oligomerization tune the physicochemical properties of n-butylammonium acetate: Cation-base clusters vs. Anion-acid dimers, *Phys. Chem. Chem. Phys.* 19 (37) (2017) 25544–25554, <https://doi.org/10.1039/C7CP04078D>.
- [48] K. Bica, R.D. Rogers, Confused ionic liquid ions - A “liquification” and dosage strategy for pharmaceutically active salts, *Chem. Commun.* 46 (2010) 1215–1217, <https://doi.org/10.1039/b925147b>.
- [49] K. Kaminski, E. Kaminska, K. Adrjanowicz, K. Grzybowski, P. Włodarczyk, M. Paluch, A. Burian, J. Ziolo, P. Lepek, J. Mazgalski, W. Sawicki, Dielectric relaxation study on tramadol monohydrate and its hydrochloride salt, *J. Pharm. Sci.* 99 (1) (2010) 94–106, <https://doi.org/10.1002/jps.21799>.
- [50] P. Sippel, P. Lunkenheimer, S. Krohns, E. Thoms, A. Loidl, Importance of liquid fragility for energy applications of ionic liquids, *Sci. Rep.* 5 (2015) 1–8, <https://doi.org/10.1038/srep13922>.
- [51] Y. Corvis, P. Négrier, M. Lazerges, S. Massip, J.M. Léger, P. Espeau, Lidocaine/1-menthol binary system: Cocrystallization versus solid-state immiscibility, *J. Phys. Chem. B.* 114 (2010) 5420–5426, <https://doi.org/10.1021/jp101303j>.
- [52] E.A. Losev, E.V. Boldyreva, A salt or a co-crystal-when crystallization protocol matters, *CrystEngComm.* 20 (16) (2018) 2299–2305, <https://doi.org/10.1039/C7CE02204B>.
- [53] Y. Yuan, L. Wang, D. Li, Z. Deng, H. Zhang, How Many Parameters Can Affect the Solid Form of Cocrystallization Products in Mechanochemical Reactions? A Case Study, *Cryst. Growth Des.* 18 (12) (2018) 7244–7247, <https://doi.org/10.1021/acs.cgd.8b01320>.
- [54] S.L. Childs, G.P. Stahly, A. Park, The Salt-Cocrystal Continuum: The Influence of Crystal Structure on Ionization State, *Mol. Pharm.* (2007), <https://doi.org/10.1021/mp0601345>.